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FKBP5 risk alleles and the development of intrusive memories

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ABSTRACT

Intrusive memories are unwanted recollections that maintain distress and are central to numerous psychological disorders, including posttraumatic stress disorder (PTSD). Convergent evidence suggests that glucocorticoid increases enhance the strength of emotional memories. The FKBP5 polymorphism modulates glucocorticoid receptor sensitivity, and has been shown to increase risk for PTSD. Healthy high and low risk FKBP5 allele carriers ($N = 46$) underwent a cold pressor task, and then viewed negative and neutral images. Two days later participants were given a surprise recall test and measure of intrusive memories of the images. Following the cold pressor task, high-risk allele participants had a higher cortisol response than low-risk participants. High-risk carriers also reported more intrusive memories of the negative and neutral images than low-risk carriers. These findings point to the minor alleles of the FKBP5 polymorphism being a risk factor for development of intrusive memories, possibly as a result of impaired glucocorticoid receptor sensitivity. This may explain one mechanism for FKBP5 being a risk factor for PTSD following traumatic events.

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1. Introduction

Intrusive memories are repetitive, unwanted sensory-perceptual recollections that are experienced involuntarily and are often associated with negative affect (Clark & Rhyno, 2005). These memories are primarily visual, however, can contain certain sounds, smells and tastes (Brewin, Gregory, Lipton, & Burgess, 2010). They are a common feature of numerous psychological disorders (Krans, Näring, Becker, & Holmes, 2009). Within clinical populations, such as people with posttraumatic stress disorder (PTSD), intrusive memories are commonly associated with high levels of distress, which may maintain cognitive avoidance (Dunmore, Clark, & Ehlers, 1999; Wenzlaff & Wegner, 2000) or rumination (Ehlers, Mayou, & Bryant, 1998; Murray, Ehlers, & Mayou, 2002). For this reason, delineation of the factors predisposing people to intrusive memories is important for clarifying the mechanisms of many psychiatric conditions.

Understanding the nature of intrusive memories has built upon the extensive literature on emotional memories, and particularly the memory modulation hypothesis, which postulates that the stress response leads to the amygdala engaging noradrenergic and glucocorticoid systems that interact to promote memory storage of emotionally arousing information (McGaugh, 2000). Consistent with the purported role of glucocorticoid modulation of memory consolidation, numerous studies have revealed that exogenous administration of cortisol selectively enhances memory for emotional over neutral stimuli (Buchanan, Brechtel, Sollers, & Lovallo, 2001; Kuhlmann & Wolf, 2006; Payne et al., 2007; van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010). Further, participants with higher endogenous levels of cortisol have significantly stronger amygdala activation in response to emotionally arousing stimuli relative to participants with lower cortisol levels (van Stegeren, Wolf, Everaerd, & Rombouts, 2008; van Stegeren et al., 2007). The memory-modulatory effects of glucocorticoids are believed to be a result of specific glucocorticoid receptor (GR) binding, as it has been shown that blocking GRs at encoding and consolidation results in memory impairment (Lupien et al., 1997).

Relevant to the role of GRs in the stress response is the GR co-chaperone protein FK506 binding protein 5 (FKBP5) which influences GR sensitivity via its impact on ligand binding, receptor activation and transcriptional processes (Scammell, Denny, Valentine, & Smith, 2001). A number of FKBP5 polymorphisms have recently been identified and found to play a role in individual stress responsivity. In response to a psychosocial stressor, healthy individuals with homozygous FKBP5 minor alleles demonstrate lower cortisol recovery and higher self-reported anxiety (Ising et al., 2008; Mahon, Zandi, Potash, Nestadt, & Wand, 2013). Polymorphisms in FKBP5 have been found to interact with the severity of childhood abuse to predict adulthood PTSD, which is characterized by intrusive memories (Binder et al., 2008; Xie et al., 2010). From an epigenetic perspective, it has been reported that people

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with the risk alleles of FKBP5 experience distinct chromatin conformations following childhood abuse, and this altered structure leads to greater GR receptivity (Klengel et al., 2013). Taken together, these studies indicate that stress-related conditions implicating overconsolidation of emotional memories are associated with FKBP5.

This study investigated the extent to which a relationship exists between FKBP5 polymorphisms, stress response and intrusive memories in a healthy sample. Based on previous studies we compared participants with high and low risk FKBP5 alleles in terms of their predisposition to develop intrusive memories. Specifically, we defined risk alleles as the minor alleles of 4 single nucleotide polymorphisms (SNPs) that have been repeatedly associated with increased risk for enhanced stress responses. The selection of these specific alleles (and the empirical basis for their selection) were: rs3800373 (increased FKBP5 protein levels, impaired HPA negative feedback following stressors, psychopathology risk following trauma; (Binder et al., 2008; Zimmermann et al., 2011), rs9296158 (impaired negative feedback of the HPA axis, association with post-traumatic stress disorder (PTSD) and depression; (Binder et al., 2008; Mehta et al., 2011; Zimmermann et al., 2011), rs1360780 (reduced basal cortisol levels, risk for PTSD and depression, attentional bias to threat; (Boscarino, 2012; Fani et al., 2013; Xie et al., 2010; Zimmermann et al., 2011), and rs9470080 (lower basal cortisol level, increased risk for PTSD, and increased amygdala reactivity; (Binder et al., 2008{Velders, 2011 #43865; White et al., 2012)}. FKBP5 gene region that have been associated with increased risk: rs3800373, rs9296158, rs1360780 and rs9470080. In line with the existing literature, it was hypothesized that high-risk FKBP5 carriers (determined by individual allele combinations) would exhibit increased cortisol responding to a stressor and would display more intrusive memories to emotional stimuli than low-risk carriers.

2. Methods

2.1. Participants and genotyping

In a testing session conducted up to one-year prior, undergraduate psychology students who reported all grandparents were of Caucasian heritage provided saliva samples in return for course credit. Samples were collected using the Oragene DNA collection kit (DNA Genotek, Ottawa, Canada) and genomic DNA was extracted. On the basis of associations between SNPs and indices of stress response (Binder et al., 2008; Xie et al., 2010), four SNPs in the FKBP5 gene region (rs3800373, rs9296158, rs1360780 and rs9470080) were selected for genotyping. Genotypes were determined using iPLEX Gold™ primer extension followed by mass spectrometry analysis on the Sequenom MassARRAY system (Sequenom, San Diego, CA) by the Australian Genome Research Facility (http://www.agrf.org.au/). Genotype frequencies in the total sample (n = 204) were as follows: rs9296158 AA = 18, AG = 88, GG = 98; rs1360780 TT = 19, CT = 86, CC = 99; rs 3800373 GG = 15, GT = 85, TT = 104; rs9470080 TT = 24, CT = 84, CC = 96. The distributions of rs4713916, rs1360780, rs 3800373, and rs9470080 did not differ from Hardy–Weinberg equilibrium (p = 0.72, p = 0.69, p = 0.72, and p = 0.66, respectively). To determine the relative effects of stress on participants who carried the risk alleles, two groups were defined: the low-risk group consisted of carriers that were heterozygous for 3 or fewer high-risk alleles; the high-risk group represented carriers who were either hetero- or homozygous for all 4 high-risk alleles, or had a combination of 4 hetero- and homozygous high-risk alleles. Participants were screened for depression and anxiety on the DASS21, and those who scored above the moderate cut-off on either scale (>6 on depression subscale or >5 on anxiety subscale; based on population norms, Lovibond & Lovibond, 1995) were not recruited into the study. In terms of the initial sample, 103 participants were categorized as low risk and 101 were categorized as high risk. Only 46 participants could be contacted the year following genetic screening (because of limited re-enrolment in the psychology program in which research was being conducted), and of these 23 were low-risk individuals (6 males, 17 females) with a mean age of 18.78 years (SD = 1.59) and 23 were high-risk individuals (8 males, 15 females) with a mean age of 19.45 years (SD = 3.29). There were no differences between allele groups in terms of sex ratio, χ^2 = 0.41, p = 0.52.

2.2. Procedure

Participants were instructed to refrain from exercising 24 h before, eating one hour before, and consuming caffeine or alcohol three hours before each experimental session to limit confounding influences on cortisol levels. Testing was conducted between the hours of 12:00 and 18:00 to minimize the effects of diurnal stress hormone variations. Following written informed consent, participants completed the DASS 21. After a period of 15 min during which participants read magazines and habituated to the testing environment, the first saliva sample was collected to measure baseline hormone levels. All participants were then instructed to undertake the CPT as described above. Immediately after the CPT, participants viewed the negative and neutral IAPS images that were presented in a slideshow lasting 3 min. A second saliva sample was collected immediately after the image presentation (for sAA analysis). After a 20-min delay period, a third saliva sample was collected (for cortisol analysis).

At 9:00 two days after the experimental session, participants were sent a link via email to an electronic questionnaire that they were required to complete on that day. The link contained instructions to complete the intrusions questionnaires, followed by the free recall test. All participants completed this task within the designated timeframe.

3. Materials

3.1. Images

Negative and neutral color images were selected from a standard set of pictures from the International Affective Picture System (IAPS; (Lang, Bradley, & Cuthbert, 2008). The IAPS is a widely used picture set that provides normative information for experimental investigations of emotion and attention. Eighteen negative images rated high on arousal and low on valence and 18 neutral images rated low on arousal and intermediate on valence were randomly interspersed in one of two fully randomized orders (with no more than two successive presentations of the same type of image). Images were presented in a slideshow for 5 s each on a 15-in. laptop using Microsoft PowerPoint software. Negative images had a mean normative arousal rating of 6.62 (SD = 2.25) and mean normative valence rating of 1.66 (SD = 1.19). Neutral images had a mean normative arousal rating of 2.33 (SD = 1.72) and mean normative valence rating of 4.81 (SD = 1.03) (Lang et al., 2008).

3.2. Cold Pressor Test (CPT)

Level of stress was manipulated by administering the CPT. The CPT involves participants immersing their forearm in a container of ice-cold water (0–4 °C) for a maximum of 3 min, with temperature gauged via a thermometer. Before the task, participants are instructed to place their dominant forearm in the water until asked to remove it. If participants remove their arm prematurely, they are informed that they must re-immerse it as soon as possible. The CPT is a widely used procedure that has been found to be effec-

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